

REMARKS

Upon entry of the present amendment, claim 1 will be canceled without prejudice or disclaimer of the subject matter recited therein; and claims 2 and 3 will be amended. Claims 2 and 3 will remain pending, with claims 3 being the sole independent claim.

By the amendment herein, claim 3 has been amended to be in independent form and claim 2 has been amended to be in method form dependent upon claim 3.

Reconsideration of the rejections of record, and allowance of the application in view of the following remarks are respectfully requested.

Claim of Foreign Priority

Applicants express appreciation for the acknowledgement of the claim of foreign priority as well as receipt of the certified copies of the priority applications. It is noted that the certified copies have been received in this national stage application from the International Bureau.

Information Disclosure Statements

Applicants also express appreciation for the Examiner's confirmation of consideration of Applicants' Information Disclosure Statement, filed June 9, 2006, by including an initialed copy the Form PTO-1449 with the Office Action.

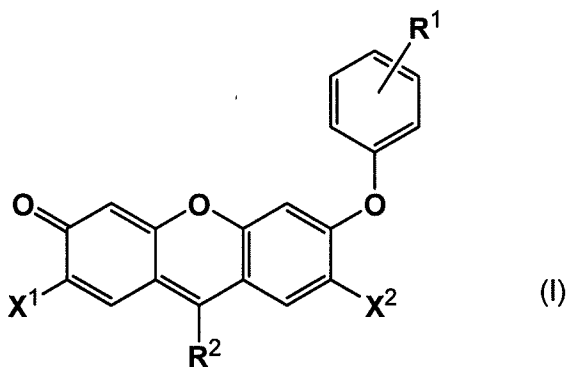
Response To Rejection Under 35 U.S.C.112, Second Paragraph

Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps including a correlation between the fluorescence and the measurement of hypochlorite.

In response to this ground of rejection, Applicants submit that the claim is definite. In particular one having ordinary skill in the art would readily understand the scope and content of the claimed subject matter, and that the claim does not omit essential steps.

In particular, claim 3 includes a method for measuring peroxynitrite, which comprises:

(A) reacting a compound represented by the following formula (I) or a salt thereof and peroxynitrite,



wherein R^1 represents a substituted or unsubstituted amino group, or hydroxy group; R^2 represents a 2-carboxyphenyl group which may be substituted; and X^1 and X^2 independently represent hydrogen atom, or a halogen atom; and

(B) measuring fluorescence of a dephenylated compound or a salt thereof produced in (A).

The rejection contends that there is a gap between the steps of claim 3. However, claim 3, in contrast to the assertion in the rejection, is directed to a method for measuring peroxynitrite, recites a reaction, and thereafter measures fluorescence of the resulting compound.

If this ground of rejection is maintained, the Examiner is respectfully requested to explain why the claim needs to recite a correlation between the fluorescence and the measure of hypochlorite when the claim is directed to measuring peroxynitrite.

Accordingly, the rejection should be withdrawn.

Art Based Rejection

The following art based rejections are set forth in the Office Action.

(a) Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 01/64664 to Nagano.

(b) Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 01/64664 (using EP 1 260 580 A1 as English version).

In response, Applicants submit that these grounds of rejection are without appropriate basis, and should be withdrawn.

Initially, Applicants note that the anticipation and obviousness rejections with respect to claims 1 and 2 are moot because the claims have been canceled.

Regarding the anticipation rejection of claim 3, the anticipation rejection is clearly inappropriate, because the obviousness rejection states that WO 01/64664 does not disclose measuring peroxynitrites. Accordingly, WO 01/64664 does not disclose each and every feature recited in Applicants' claim 3 whereby the anticipation rejection should be withdrawn.

Regarding the obviousness rejection of claim 3, as discussed in Applicants' originally filed specification, beginning at page 1, third full paragraph, peroxynitrite (ONOO^-) is a typical substance among RNS, and is produced by a reaction of NO and superoxide. Reaction rate of this production reaction is mostly limited by diffusion, and when superoxide produced by

NADPH oxidase or the like and NO produced by NO synthetase (NOS) coexist, ONOO⁻ is immediately produced. ONOO⁻ has high oxidation ability, for example, it achieves hydroxylation of an aromatic ring, and has characteristic reactivities such as, for example, efficient nitration of tyrosine.

It is further disclosed that examples of the methods for detecting ONOO⁻ developed so far include (1) a method of performing staining by using an antibody directed to nitrotyrosine produced by nitration of tyrosine, and (2) a method of detecting singlet oxygen produced by reaction of ONOO⁻ and H₂O₂ on the basis of light emission at 1.3 μm. It is disclosed that although method (1) achieves high specificity and has been widely used, the method has a problem in that ONOO⁻ cannot be detected in real time by applying the method to a living cell system, because staining should be performed with antibodies. In addition to the aforementioned two methods, it is also disclosed that (3) a chemiluminescence method using luminol, and (4) a fluorometric detection method using a fluorescence probe to detect overall active oxygen species such as 2',7'-dichlorodihydrofluorescein (DCFH) have been used. However, these methods fail to achieve specificity, and therefore reliable detection cannot be expected even if various inhibitors are used. For example, it is disclosed that in the method (4), DCFH reacts with both of NO and superoxide to give an increase in fluorescence, and therefore it is impossible to distinguish whether ONOO⁻ is detected, or NO or superoxide is detected.

Reference is also made in the originally filed application to W0 01/64664 for the fact that arylated fluorescein derivatives are known to be useful reagents for measuring active oxygen (International Patent Publication WO01/64664). However, it is disclosed that this publication neither suggests nor teaches that the fluorescein derivatives have reactivity with peroxynitrite.

Still further, attention is directed to Applicants' Examples wherein the results are shown in Table 1. As disclosed in Example 1, the measuring reagents of the present invention (HPF and APF) gave an increase in fluorescence by the reaction with peroxynitrite, whilst the reagents did not react with superoxide nor NO, and gave substantially no increase of fluorescence. DCFH greatly increased fluorescence by the reaction with peroxynitrite, and it also increased fluorescence by the reactions with both of superoxide and NO. These results are disclosed as revealing that peroxynitrite alone is successfully measured specifically by using the measuring reagent of the present invention without being affected by superoxide or NO.

In contrast, to the showings in Applicants' originally filed application, WO 01/64664, which is specifically discussed in Applicants' originally filed application and includes the inventors of the present application, WO 01/64664 does not teach or suggest a method of measuring peroxynitrite, nor does WO 01/64664 teach or suggest a method of measuring peroxynitrite without being affected by NO or superoxide.

The rejection does not refer to claim 3, but to claim 4, and this is apparently a typographical error with claim 3 being intended. However, the rejection does not point to any teaching as to the desirability of measuring peroxynitrites. The rejection points to Table 1 of WO 01/64664, but does not indicate how Table 1 teaches or suggests the measurement of peroxynitrites, or the surprising capability of measuring peroxynitrites without being affected by NO or superoxide.

If the rejection is maintained, the Examiner is respectfully requested to indicate any teaching or suggestion in the prior art of record to arrive at Applicants' claimed subject matter. In this regard, the Examiner is reminded that the basis for the rejection must be arrived at from the prior art and not from Applicants' disclosure.

Response To Obviousness-Type Double Patenting Rejections

The following obviousness-type double patenting rejections are set forth in the Office Action.

(a) Claims 1-3 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 and 10-14 of U.S. Patent No. 7,087,766

(b) Claims 1-3 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2 of U.S. Patent No. 7,378,282.

With regard to these grounds of rejection, Applicants initially note that Patent No. 7,087,766 is the national stage of WO 01/64664. Accordingly, for at least the reasons set forth above, U.S. Patent No. 7,078,766 does not render obvious the subject matter recited in Applicants' independent claim 3 and claim 2 dependent therefrom.

This further, the claims 1-5 and 10-14 of U.S. Patent No. 7,087,766 are merely directed to the compound or to measurement of reactive oxygen, and claims 1 and 2 of U.S. Patent No. 7,378,282 are directed to hypochlorite ion. The claims of U.S. Patent No. 7,087,766 and U.S. Patent No. 7,378,282 do not teach or suggest any desirability of measuring peroxynitrites or the surprising capability of measuring peroxynitrites without being affected by NO or superoxide.

Applicants therefore submit that the rejections of record are without appropriate basis and should be withdrawn.

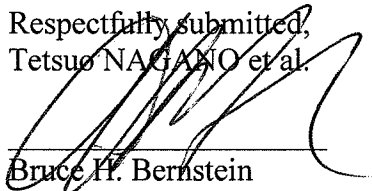
CONCLUSION

In view of the foregoing, the Examiner is respectfully requested to reconsider and withdraw the restriction requirement and the rejections of record, and allow each of the pending claims.

Applicants therefore respectfully request that an early indication of allowance of the application be indicated by the mailing of the Notices of Allowance and Allowability.

Should the Examiner have any questions regarding this application, the Examiner is invited to contact the undersigned at the below-listed telephone number.

Respectfully submitted,
Tetsuo NAGANO et al.



Bruce H. Bernstein
Reg. No. 29,027

April 9, 2009
GREENBLUM & BERNSTEIN, P.L.C.
1950 Roland Clarke Place
Reston, VA 20191
(703) 716-1191

Arnold Turk
Reg. No. 33094